MEDICAL PROCEEDINGS

MEDIESE BYDRAES

A South African Journal for the Advancement of Medical Science

'n Suid-Afrikaanse Tydskrif vir die Bevordering van die Geneeskunde

Registered at the General Post Office as a Newspaper

By die Hoofposkantoor as Nuusblad Geregistreer

Vol. 5 · No. 20 · 5s. | Johannesburg 3 October 1959 Oktober 3 | Jaarliks £1 : 1 : 0 Yearly

IN THIS ISSUE · IN HIERDIE UITGAWE

Publishers: Juta and Co. Ltd. P.O. Box 1010 · Johannesburg: P.O. Box 30 · Cape Town ● *Uitgewers:* Juta en Kie. Bpk. Posbus 1010 · Johannesburg: Posbus 30 · Kaapstad

Medical Proceedings · Mediese Bydraes

Vol. 5 · No. 20 INDEX · INHOUD 3 October 1959 Oktober 3

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P.O. Box 1010 · Johannesburg | Posbus 1010 · Johannesburg

Editor : Redakteur

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Vol. 5 | 3 October 1959 Oktober 3 | No. 20

EDITORIAL · REDAKSIONEEL

THE TESTING OF NEW DRUGS

DIE TOETS VAN NUWE GENEESMIDDELS

'The Proper Study of Mankind is Man.' *Pope*

In London recently, at the Royal Society of Medicine, a symposium was held on *Progress in the Evaluation of Drugs*. This provided a most useful opportunity for a 'free interchange of ideas.' Considerable attention was paid to the importance of the clinical trial and pilot trials on human subjects after thorough animal experimentation.

Shortly after the London meeting, an all-day symposium on *The Clinical Evaluation of Drugs* was held at the Albert Einstein Medical Center, Philadelphia.

Although much of the same ground was covered as at the meeting in London, discussion ranged more widely and included the teaching of clinical pharmacodynamics, the short life of new products and considerable emphasis on the use of the double-blind technique in assessing the efficiency of new products.

The interesting statement was reported that part of the difficulty of evaluating results of human experiments is due to the fact that some subjects may be enthusiastic 'placebo reactors,' whereas 'other more pessimistic persons will underreact to that which is really good or bad for them.'

The role of statistics appeared to be regarded as a necessary evil. However, one thing is quite certain. If statistics must be employed, the statisticians should be consulted in the

Die *Royal Society of Medicine* het onlangs in Londen 'n simposium gehou oor *Vordering met die Waardebepaling van Geneesmiddels*. Dit het 'n uiters nuttige geleentheid vir 'n vrye meningswisseling verskaf. Heelwat aandag is geskenk aan die belangrikheid van kliniese proefnemings en van eerste proefnemings met mense as onderwerpe nadat deeglike proefnemings met diere gedoen is.

Kort na die Londense byeenkoms is 'n heeldag lange simposium oor die *Kliniese Waardebepalings van Geneesmiddels* in die Mediese Sentrum Albert Einstein, Philadelphia, gehou.

Ofskoon baie van dieselfde terrein hier gedek is as op die vergadering in Londen, was die besprekings omvattender en het dit ingesluit onderrig in die kliniese farmakodinamiek, die kort lewensduur van nuwe produkte en aansienlike beklemtoning van die gebruik van die dubbelblind-tegniek om die doeltreffendheid van nuwe produkte te bepaal.

Die interessante verklaring is gedoen dat deel van die moeilikhede met die waardebepaling van die resultate in proefnemings met mense te wyte is aan die feit dat sommige voorwerpe geesdriftige 'placebo-reaktors' is, terwyl ander, 'meer pessimistiese persone minder sal reageer op wat werklik goed of sleg vir hulle is.'

Die rol van statistiek word skynbaar as 'n noodsaaklike euwel beskou. Maar een ding

planning of the experiment and not merely referred to when the task of interpreting the data has to be faced.

The increased tempo at which new drugs are being developed has brought very much to the fore the crucial importance of well-planned clinical trials carried out with integrity and preferably by independent investigators.

The evaluation of the clinical efficacy of drugs in Man is well known to be notoriously difficult. Our medical schools and our hospitals can therefore make a great contribution in this regard by participating in these evaluations on a co-operative basis. By the time a new drug reaches the stage of clinical trial, pharmaceutical and pharmacological research has done all that is humanly possible to discover its properties by exhaustive experiments on animals. The final stages of the assessment on human beings for the treatment of disease are therefore reached when the request for a trial can be made with reasonable certainty that there is no danger. Only in this way can the safety as well as the therapeutic efficacy of a new product be established.

South Africa has already made useful contributions by co-operating in this type of clinical research. Indeed, the fact that we have been asked to help implies at once a tribute to and a recognition of our standards of medical practice as equal to those anywhere else in the world.

bly absoluut seker. As stististiek gebruik moet word dan moet statistici geraadpleeg word oor die planne vir die proefnemings en moet daar nie net na hulle verwys word wanneer die taak om die besonderhede te vertolk, afgehandel moet word nie.

Die toenemende tempo waarteen nuwe middels ontwikkel word, het die uiterste belangrikheid van goed-beplande kliniese proefnemings wat uitgevoer word met integriteit en verkieslik deur onafhanklike navorsers, ten sterkste op die voorgrond gebring.

Dis bekend dat dit besonder moeilik is om die waarde van die kliniese uitwerking van geneesmiddels in die mens te bepaal. Ons mediese skole en ons hospitale kan dus in hierdie opsig 'n groot bydrae lewer deur op koöperatiewe grondslag aan hierdie waardebepalings deel te neem. Teen die tyd dat 'n nuwe geneesmiddel die stadium van kliniese proefneming bereik, het die farmaseutiese en farmakologiese navorsers reeds alles wat menslik moontlik is gedoen om die eienskappe daarvan met deurtastende proefnemings op diere te ontdek. Die eindstadium van die berekening van die waarde wat dit het vir die behandeling van siektes by mense word eers dan bereik wanneer met 'n redelike mate van sekerheid dat geen gevaar bestaan nie versoek kan word dat proefnemings gedoen word. Alleen op hierdie wyse kan sowel die veiligheid as die terapeutiese werksaamheid van 'n nuwe produk vasgestel word.

Suid-Afrika het reeds waardevolle bydraes gelewer deur saam te werk met dié soort kliniese navorsing. Die feit dat ons gevra word om te help is, om die waarheid te sê, nie alleen 'n huldeblyk aan nie maar ook 'n erkenning van die hoë standaard van ons mediese praktyk wat aan dié op enige ander plek in die wêreld gelykstaan.

PORPHYRIA AND THE ANAESTHETIST

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The pre-operative diagnosis of porphyria is of great importance to the anaesthetist because of the frequent use of intravenous barbiturates, which invariably precipitate an acute attack in the susceptible individual. It is of particular importance in South Africa where the disease has been demonstrated in many of our Afrikaans families.

Porphyria is a disturbance in the metabolism of the pyrrole pigments, resulting at times in a marked increase in the excretion of porphyrins in the urine and characterized by cutaneous, psychological and neurological symptoms. In the quiescent stage the only sign may be increased sensitivity of the skin, particularly to sunlight. The acute attack is characterized by abdominal pains, vomiting and hysteria. After a few days a peripheral neuritis may develop, with various degrees of paralysis and the patient may die. The urine is reddish-brown due to contained porphyrins.

Dean has shown that European descriptions of the disease and their division into 'chronic cutaneous porphyria,' 'symptomless porphyria' and 'acute porphyria' are different manifestations of the same inherited disorder.[1, 5] Acute porphyria is common in Sweden and 200 cases have been described, but it is a different genetic condition from that seen in South Africa.[6, 7] Up to July 1955 Dean had treated 21 cases of acute porphyria, 3 of which died.[1, 2] Barnes (in 1951) described 40 cases in South Africa.[2] The incidence of porphyria in the Eastern Cape Province is 1%.[1]

ETIOLOGY

Very small quantities of porphyrins are excreted in health in the urine and faeces; slightly increased excretion occurs in a number of diseases and grossly increased excretion accompanies porphyria.

Haem (relatively abundant in the body as part of haemoglobin, myoglobin and several intracellular enzymes) is an iron-porphyrin complex. Apart from small quantities of faecal porphyrin formed in the gut by the action of digestive enzymes on ingested haem pigments, the excreted porphyrins are not derived from the catabolism of haem. Rimington suggests that, during synthesis of the haem pigments, a very small quantity of type I porphyrin is produced and eliminated from the body.[3, 4] Also the reticulum material extruded from maturing erythrocytes is probably another source of excreted porphyrin. Total daily excretion of coproporphyrin in health is 0–0.1 mg. in urine and 0.3 mg. in faeces.

In a variety of conditions, e'g' liver disease, pernicious anaemia, fevers, infections and following absorption of chemicals and metals such as sulphonamides, benzene ring compounds, lead, selenium and arsenic, up to 50 times the normal amount of porphyrin may be excreted. In porphyria up to 100 mg. may be excreted in 24 hours.

It is thought that the disease results from an over-production of porphyrins during haemoglobin synthesis. It is not known whether the symptoms are due to an intoxication from the excess porphyrins present. However, polyneuritis has been produced by injections of haematoporphyrin, and histological studies suggest that the polyneuritis of porphyrinuria has a toxic etiology.[8] Injections of porphyrins have also given rise to excessive skin sensitivity, especially to sunlight.

Porphobilinogen, which is found in the urine of porphyrics, is a monopyrrolic precursor of uroporphyrin, coproporphyrin and protoporphyrin.

THE INHERITANCE OF PORPHYRIA

Dean and Barnes[5] traced the genealogies of 32 porphyric family groups, all of old burger stock. A total of 324 members (168 male and 156 female) had clinical manifestations of porphyria. One of these family groups was intensively studied, the urine and faeces being examined for porphyrins. The founder of this family came to South Africa from Holland in 1713; his wife's family had come in 1688. His great-grandson, born in 1788, had 4 sons and 1 daughter. The third son (born in 1814) had 478 descendants—434 of whom are still alive. They were all traced. The authors concluded that porphyria was inherited as a non-sex-linked Mendelian dominant and that, if one parent was a porphyric, half the descendants would inherit the disease.

Skin sensitivity appears to be more common in men and acute porphyria and abdominal symptoms more common in women.

Prophyria has been described in non-Europeans by Barnes, who studied 113 cases found among the Bantu races on the Witwatersrand.[9] A third of the cases sought medical aid because of skin lesions and the rest were discovered accidentally. Tribes from all over the Union were affected and the disorder was not found until adolescence.

A very rare form of congenital porphyria with marked skin sensitivity to light from birth, pink staining of teeth and bone, and with anaemia and splenomegaly is inherited as a Mendelian recessive characteristic. This was described in Sweden by Waldenstrom and has not been seen in South Africa,[6, 7] except possibly for the case described by Barnes[9] in a Bantu female.

SIGNS AND SYMPTOMS

One must differentiate between hyperporphyrinism (e.g. due to liver dysfunction) and porphyria which is of genetic origin, because the former cases are not affected by drugs.[13]

It usually causes no symptoms in children. In adults there is the quiescent stage and the acute attack.

1. QUIESCENT STAGE

During this period the patient may come in to hospital for an operation entirely unrelated to the disease. Certain points should put the anaesthetist on his guard:

(*a*) The patient's name. In South Africa the names van Rooyen and Ferreira should raise suspicion.

(*b*) *Cutaneous manifestations.* Usually there is a slightly increased sensitivity of the exposed skin (on the back of hands and face) which blisters and abrades easily; scars may be found on the backs of the hands. The blisters, when they occur, are usually about half an inch in diameter. They rupture and leave an ulcer. Eventually the hands may be scarred from many healed lesions.

The skin sensitivity is generally more pronounced in men. If the skin on the back of the hand is scraped 4 or 5 times with a finger-

nail, in porphyria the superficial layer will abrade. Pigmentation often occurs in porphyrics and women may show pre-auricular hypertrichosis. Careful enquiry may reveal that relatives also suffer from a sensitive skin. If cutaneous manifestations are present, porphyrins can be detected in the urine by spectroscopic examination and by fluorescence in ultra-violet light.

Male porphyrics, apart from skin manifestations, may remain well throughout life unless they are given barbiturates or a thiopentone anaesthetic.

(*c*) *Abdominal Discomfort.* This is the usual complaint in female porphyrics and, as they are often given sedative barbiturates as treatment, the condition may be aggravated or an acute attack precipitated. Appendicitis, intestinal obstruction or some gynaecological condition may be diagnosed and the patient subjected to a laparotomy with thiopentone anaesthesia, with fatal results. Female porphyrics often appear emotionally unstable. *Pregnancy* accentuates these symptoms and there may be a history of previous pregnancies being terminated because of pains, vomiting and hysteria.[1]

In the differential diagnosis one must consider Addison's disease, hysteria, mental disorder and hyperthyroidism. If in doubt, examination of the urine and faeces will verify the diagnosis.

2. ACUTE ATTACK

Dean states that in his experience it is always precipitated by drugs, especially barbiturates, chemicals, or alcohol.[1] Acute attacks are more common in women, probably because they take more sedatives. Attacks also occur during pregnancy.

During an attack the patient is emotionally upset and complains of severe pains all over the body, especially in the abdomen. He may exhibit a toxic delirium simulating delirium tremens. If there is vomiting with abdominal tenderness, distension and rigidity, the patient may have a laparotomy performed. It is, therefore, the duty of the anaesthetist to enquire about the result of urine examination in all cases presenting as examples of an acute abdomen. The urine is reddish-brown in colour and darkens on standing. A great excess of porphyrin and porphobilinogen will be present.

If the condition is correctly diagnosed, within a few days there will develop a lower motor neurone paralysis of the extremities with loss of reflexes due to peripheral neuritis. The pupils are dilated, there is a tachycardia and the blood pressure is raised. If the patient survives the peripheral neuritis persists for months. During an acute attack there is evidence of impaired liver function and usually a leucocytosis. The cerebrospinal fluid is normal. There may be an ascending paralysis of the Landry type (which may lead to bulbar palsy and death) and convulsions.

PORPHYRIA IN THE BANTU

Barnes[9] found certain differences from the European cases. Unfortunately he could only demonstrate a familial incidence in a few cases, due to the difficulty of tracing relatives. Acute porphyria is rare in the Bantu and Barnes only mentions 2 cases. Skin lesions are common and, in contrast to Europeans, are commoner in females. In general the lesions are the same as in Europeans and porphyrins have been demonstrated in the 'blisters'. Sometimes a generalized hyperpigmentation of face and hands is seen. Hypertrichiosis, limited to temporal and pre-auricular regions, is not uncommon and very striking when present in females. The disease is commonly mistaken for pellagra which is, of course, often seen in the Bantu. It was at one time suggested that there were increased porphyrins in the urine in pellagra (Beckh), but Rimington and Leitner have refuted this.[4] Syphilis must also be considered in the differential diagnosis.

In about half of Barnes' cases there was a hepatomegaly. In view of the frequence of hepatomegaly in the Bantu associated with malnutrition, he had difficulty in deciding what relation this had to the porphyria. It has been shown by Garrod that there is increased excretion of porphyrins in liver disease and it is possible that some of the cases showing faint traces of porphyrin could have been the result of liver disease.[10] Temporary hyperporphyrinism due to liver dysfunction may be difficult to distinguish from the genetic condition in the absence of an adequate history.

In December 1950, Barnes and Findlay described a case of congenital porphyria in a 13-year-old Barolong girl with 'pink-staining' of the teeth, etc. This is the excessively rare type inherited as a Mendelian recessive gene.[11]

OPHTHALMOLOGICAL CHANGES IN PORPHYRIA

Barnes and Boshoff[12] have described this condition. There is light sensitivity of the skin giving hydroea vacciniforme and hydroea aestivale of the eyelids. There may be photophobia and conjunctivitis with pus. A herpetiform keratitis has been described and also scleritis with scleromalacia perforans. Some

cases show limbal phlyctenules. The fundus is oedematous with black pigmentation and haemorrhages.

CHEMISTRY OF HAEM

Haem is Iron-Protoporphyrin IX.

Porphobilinogen is the monopyrrolic precursor of uro-, copro- and protophorphyrin.

Uroporphyrin, coproporphyrin and protoporphyrin are found in human tissues and have methyl groups substituted in positions 1, 3, 5 and 7. Uroporphyrin and coproporphyrin belong to series I and protoporphyrin to series III.

CHEMISTRY OF THE PORPHYRINS[18]

Pyrrole Pigments. A large number of animal pigments containing pyrrole nuclei are known.

Four substituted pyrrole nuclei are joined together through methinyl (=CH−) or methylene (−CH_2−) groups to form a chain or ring:

i. *Chain Type*: *The Bile Pigments*: —
Verdohaemochromogen;
Biliverdin;
Bilirubin;
Urobilin.

ii. *Ring Type*: *The Porphyrins*: These have the property of combining with metals and proteins to give pigments active in the carriage of respiratory gases or in oxidation-reduction systems:
Haemoglobins;
Haemochromogens;
Cytochromes;
Haematin;
Haem.

Protoporphyrin, coproporphyrin and uroporphyrin are derived from *porphobilinogen*—a monopyrrolic precursor.

The chlorophylls are also porphyrin derivatives.

Haem is an iron-containing porphyrin known as iron-protoporphyrin IX. The porphyrin nucleus consists of 4 pyrrole rings joined together by 4 methine (=C−H−) bridges. They are thus tetrapyrrols.

EXAMINATION OF URINE AND FAECES FOR PORPHYRINS

It is important to examine both urine and faeces,[1] for when the diagnosis is in doubt examination of the faeces for increased porphyrin excretion is of the greatest value. This examination should, in doubtful cases, be done by a biochemist trained in porphyrin analysis.

Naked-Eye Appearance. In the acute stage the urine may immediately suggest porphyria because of its reddish-brown colour. It darkens considerably on standing, particularly after the addition of hydrochloric acid.

Watson-Schwartz Test. This is a test for porphobilinogen. Ehrlick's aldehyde saturated with sodium acetate should be added to 5 ml. urine and the mixture shaken with chloroform. When porphobilinogen is present a purple colour will remain in the aqueous layer.

Spectroscopic Examination. The increase in porphyrin excretion may be so slight that it can only be detected by careful spectroscopic examination of a layer several inches deep. The characteristic bands of porphyrin can then be detected by those experienced in this type of examination.

Examination in Ultra-violet Light. This method is less sensitive than is spectroscopic examination. In positive cases the urine or faeces will show brilliant red fluorescence while normal faeces show a green or a slight pink fluorescence.

In suspected cases, 4 oz. urine with a few drops of chloroform added as preservative and a sputum jar half full of faeces should be sent to a biochemist for examination.

TREATMENT OF THE ACUTE ATTACK

This has been outlined by Dean.[1]

1. Stop all drugs and sedatives—as they may be aggravating the condition.
2. Keep the patient out of the sun.
3. Good nursing is required in a private ward because of the element of hysteria.
4. If antibacterial drugs have to be given, avoid sulphonamides, but penicillin can be given safely.
5. Maintain the patient's general condition and, if there is vomiting, the nutrition and electrolyte balance must be watched and maintained by parenteral therapy.
6. To counteract the liver damage often present, a high-protein, high-carbohydrate diet with a liberal supply of vitamins must be given.
7. ACTH and cortisone may be of value;[1] 25 mg. of cortisone can be given 6-hourly for 2–3 days, and half this dose for a similar period.
8. Convulsions: 30% ether in oil is given by rectal drip, after which the rectum must be irrigated with normal saline. Epanutin may also be given (1½ gr. 6-hourly) by stomach tube.
9. Physiotherapy is indicated during recovery from the paralyses.
10. Dean stresses the practitioner's responsibility of investigating all affected family groups and giving them each a letter warning all subsequent medical attendants of their disease and the danger of drugs, especially barbiturates and sulphonamides.

THE RELATION OF DRUGS TO PORPHYRIA AND THE CHOICE OF ANAESTHETIC

Agent: Although all the authorities consulted agree that drugs can precipitate an acute attack of porphyria, there seems to be a general reluctance to state specifically which drugs must be

avoided. Amongst others, the following drugs have been mentioned as definitely precipitating acute attacks:

Barbiturates;
Sulphonamides;
The Sulphones (Sulphonal and Trional);
Alcohol;
Lead.
Isopropyl acetyl carbamide (Sedormid, Roche).

The difficulty is in knowing which drugs can be safely used for securing sedation or analgesia. Dundee and Riding state that opiates, chloral hydrate, paraldehyde and intravenous procaine 0.2% are quite safe.[14] In a personal communication from Dean he states that 'these patients tolerate pethidine and morphia fairly well, but being unstable individuals they can easily become drug addicts.' He says he has given porphyrics pethidine post-operatively without ill effects. Dean states that it is unknown as yet which drugs are definitely harmful to porphyrics. Tudor-Hughes treated an acute case associated with pregnancy with pethidine, but the patient died.[15]

An interesting observation in regard to the pain of porphyria, made by Carrié, is that porphyrics are spasmogenic.[19] Reitlinger and Klee[20] have shown that dilute solutions of coproporphyrin caused prolonged tonic spasm of isolated guinea pig intestine, refractory to atropine, but relaxed by adrenaline. In human subjects, however, adrenaline has persistently failed to relieve abdominal pain associated with smooth muscle spasm in the colon. On the other hand, sympathetic ganglion-blocking agents have produced dramatic relief and in one case splanchnicectomy had a beneficial effect.[16] This suggests an autonomic disturbance rather than a direct smooth muscle effect.

In view of these observations it seems reasonable to use sympathetic ganglion-blocking agents for the treatment of abdominal pain in porphyria. In fact, tetraethylammonium chloride (Etamon) has been used with relief of pain in these cases.[21]

If one has to anaesthetize a known porphyric, there is actually little difficulty in the choice of the anaesthetic. Everyone seems agreed that ether is quite safe. In fact, it is

TABLE 1: PORPHYRIA

I. *Congenital Type:* (Inherited as a Mendelian recessive).	1. Very rare. 2. Not seen in South Africa. (Barnes has described one case in a Bantu). 3. Marked light sensitivity from birth. 4. Dark-coloured urine. 5. Anaemia and splenomegaly. 6. Pink staining of teeth.
II. *Porphyria in South Africa:* (Inherited as non-sex-linked Mendelian dominant).	1. *Quiescent Stage:* (*a*) *Cutaneous Manifestations.* (Mainly in men. Common in Bantu especially in women). (*b*) *Abdominal Discomfort.* (Mainly in women). Accentuated by *pregnancy.* (*c*) Porphyrins may or may not be demonstrated in urine and faeces. 2. *Acute Attack:* (More common in women). (Rare in Bantu). (*a*) *Emotional upset.* (May be diagnosed as hysteria). (*b*) *Acute abdominal symptoms.* (*c*) *Peripheral neuritis* with paralysis, coming on after a few days. (*d*) *Reddish-brown urine* due to excess porphyrin and porphobilinogen. The acute attack may be precipitated in patients in the quiescent stage by drugs, especially barbiturates and sulphonamides, Sulphonal and Trional, Alcohol, Lead, 'Sedormid' (Roche).
III. *Swedish Type of Porphyria Hepatica:* (Inherited as non-sex-linked Mendelian dominant).	
IV. *Hyperporphyrinism:*	Increased porphyrin excretion. May be due to liver dysfunction. Not affected by drug as in genetic porphyria.

used to treat the convulsions associated with acute porphyria. Of inhalational agents nitrous oxide is also innocuous, but nothing is known about the safety or dangers of the others. No work has been done on the effects of relaxants, but I have personally used Flaxedil in a few suspected cases with no ill effects. Thiopentone (together with all barbiturates) is, of course, absolutely contra-indicated. There seems to be no contra-indication to local, regional or spinal anaesthesia.

EXPERIMENTAL PORPHYRIA

Schmid and Schwartz have produced experimental porphyria in rabbits, rats and mice by continued administration of the semicarbamide 'Sedormid'.[16] Dogs are also affected, but much less markedly. This may prove a valuable tool in the further study of porphyrin metabolism and chemistry.

No original work has yet been done on the effects of anaesthetic agents on the porphyrin metabolism of normal and porphyric individuals. It has been suggested by Dr. O. V. S. Kok that we should induce a disturbance in the porphyrin metabolism of dogs by means of Sedormid, i.e. corresponding to the quiescent stage of porphyria in humans, and then note the effect of anaesthetics on their metabolism. In this way we may be able to collect valuable information about the little known subject of the action of drugs in porphyria.

Perold has described cases of porphyria in cattle which were inherited as recessive genes. The disease was traced to a porphyric bull which was owned by a farmer in Swaziland.[17] A veterinary officer at Onderstepoort, P. J. J. Fourie, in association with Rimington, has reviewed the occurrence of porphyria in cattle.

SUMMARY

Table 1 summarizes the position relating to porphyria.

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THE TREATMENT OF GASTRO-ENTERITIS

A CLINICAL TRIAL OF FURAZOLIDONE

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Medical practice at sea is not very much dissimilar from that conducted by general practitioners who work in isolated areas or who do not have intimate contact with hospital and laboratory facilities. Accordingly, the results of the clinical trial of a new preparation by a medical officer in a ship at sea will be comparable with similar trials in general practice.

The substance of this communication is based on a clinical trial of furazolidone ('Furoxone') used in the treatment of gastro-enteritis in patients on board ship. The conditions at sea are similar to those one would have encountered in a community where the clinical impression of a practitioner on the value of a drug is based on his previous ex-

perience with drug therapy and with the diseases treated.

The treatment of diarrhoea is not usually difficult. If it is possible to have a laboratory report on the stools, together with a report on the sensitivity of any pathogens present to the recognized drugs available for treatment, then, of course, a specific form of therapy can be instituted. When, however, no such reports are available the practitioner must prescribe treatment with the knowledge that a considerable number of patients will certainly require more than just a medicine which contains opium, kaolin or other non-specific constituents. It must also be remembered that, as it is often impossible to isolate the causative organism in diarrhoea or to await the results of sensitivity tests, treatment has to be initiated when the patient is first seen. As a rule, depending on one's clinical assessment of the case and the necessity for the patient to be rapidly returned to full employment, the practitioner will often prescribe an antibiotic or one of the sulpha group of drugs, confident that if pathogens are present in the stool they will probably be controlled by these active compounds. This is common practice and it is not necessary to defend this procedure. There are, however, other considerations.

Although both antibiotics and sulpha drugs are widely used in the treatment of enteritis, neither class of drug is completely satisfactory. Antibiotics are costly and the doctor who prescribes them for what may be a minor, though unpleasant, complaint must also weigh the benefits to be expected against the risk of producing resistant strains of bacteria. Sulphonamides are usually prescribed in large numbers of tablets, and in addition to the inconvenience of administration, there is always the risk of toxic effects which are not, of course, negligible.

To be acceptable in the treatment of enteritis a drug should act rapidly, be effective in small dosage, not have to be given too often during the 24-hours and, if possible, not only be relatively free from side effects but should also not have the properties of producing resistant strains of pathogens in the stools. Furoxone had been made available for the treatment of diarrhoea and there was evidence to show that it was bactericidal, had almost no side effects and that resistance was not developed by organisms in the stool.

The anti-microbial activity of 'Furoxone' has been studied by Yurchenco *et al.*[3] and Rogers *et al.*[2] They reported that it was an effective bactericidal agent against the common enteric pathogens including salmonella and shigella, *B. coli, B. aerogenes, B. alkaligenes* and *Streptococcus aureus*. It has been used in veterinary medicine since 1952, but only recently has it been introduced into clinical practice. Ponce de Leon[1] used the drug in children suffering from acute bacterial disease and reported excellent results in 25 of 30 cases. The drug was well tolerated and there were no undesirable effects. Rowell *et al.*[4] subjected the drug to a clinical trial with adequate laboratory facilities and reported that 56 patients treated were rapidly restored to normal. 71 cases of acute diarrhoea occurring on board a ship at sea on voyages to the Far East and back to the U.K. have been treated with 'Furoxone' and the results of this trial are reported.

METHODS

'Furoxone' was available in 2 forms: tablets containing 100 mg. of the drug, and a liquid form which contained no other anti-diarrhoeic constituents. Adult patients were given 100 mg. 4 times a day in the 24 hours. Children of 5 years or more received 50 mg. 4 times in the 24 hours. The suggested dose for infants was 2.5 mg. per lb. of body weight in 4 divided doses in the 24 hours.

All the patients who sought treatment were seen in the acute stages of the disease. No other form of therapy was prescribed, but the patients were instructed to take adequate quantities of fluids and not to eat for 12–18 hours. Special record cards were kept for each patient and information on diet, abdominal pain, abdominal tenderness, nausea, vomiting and the number of stools passed per day were recorded and used in the asssessment of the patient's progress.

The results of therapy in acute enteritis are readily assessed. In this trial the results were evaluated on:

(*a*) The clinical condition of the patient;

(*b*) The number of stools passed in the first 24 hours;

(*c*) The number of stools passed on the 3rd day of treatment; and

(*d*) The number of days on treatment needed to obtain a clinical cure.

Where possible, a follow-up was made on the clinical state of the patients treated.

RESULTS

Table 1 presents the results obtained in the 71 patients investigated. The ages of the patients varied from 1¼ years to 54 years with an average of 30¼ years. A considerable number of patients was Asiatic, but the response to treatment was independent of racial origin. Only 3 patients failed to respond within 5 days to treatment, whereas 68 were clinically cured within 3 days. Within the first 24 hours of therapy most of the patients felt very much better and by the end of the second day were eating and drinking, although the number of stools may still have been above the normal.

TABLE 1: THE EFFECT OF 'FUROXONE' (FURAZOLIDONE) IN 71 PATIENTS SUFFERING FROM DIARRHOEA

No. of patients	*No. of Stools 1st day*			*No. of Stools 3rd day*			*Clinical Cure Days*			*Patients not Cured*
	Minimum	*Maximum*	*Average*	*Minimum*	*Maximum*	*Average*	*Minimum*	*Maximum*	*Average*	
71	3	16	6·3	0	5	1·1	2	5	3·0	3

The course of treatment was 400 mg. a day for 3 days. If after 3 days the condition still persisted, it was suggested that an alternative form of treatment should be prescribed. In only 3 patients was this necessary, one of whom had dengue fever and was sent to hospital.

Side Effects. The side effects of 'Furoxone' have been described as nausea, vomiting and headache. Since these are usually present in acute gastro-enteritis and may be due to toxaemia, it is very difficult to assess the incidence of side effects. As a rule, the majority of patients were symptom-free within 48 hours of treatment and then side effects were nil to negligible. The urine is often coloured yellow, as 'Furoxone' is rapidly excreted, but apart from telling patients about it, this is of no consequence.

DISCUSSION

The assessment of the value of an anti-bacterial agent in the treatment of gastro-enteritis is often difficult since many patients may be cured within 4 or 5 days without any specific or, indeed, any form of treatment. Nevertheless, it is common experience that anti-diarrhoea treatment will shorten the attack in most patients and will certainly enhance their morale and comfort.

In the present series, of the 71 patients treated, 68 were completely cured within 3 days and it is the writer's impression that this is a most satisfactory result in a group of patients where, even though the bacteriology of the stools was unknown, a guess could be hazarded that pathogens were probably often present and were successfully inhibited by 'Furoxone.'

A clinical trial of this nature is open to criticism because the bacteriology of the stools of the patients had not been investigated. In general practice the doctor does not often send stools for laboratory examination unless an epidemic is present in his district. He usually has to treat his cases of diarrhoea without recourse to previous scientific investigation. In this trial this is what I have done and it is my clinical impression, in relation to my experience with antibiotics and the sulpha drugs, that 'Furoxone' is a valuable form of treatment for gastro-enteritis and is singularly free from side effects. It is acceptable to patients from the point of view of convenience and ease of administration.

SUMMARY

1. Seventy-one patients suffering from gastro-enteritis have been subjected to a clinical trial with Furazolidone ('Furoxone') in a ship at sea.

2. Sixty-eight responded successfully to treatment within 3–5 days of starting therapy.

3. It is suggested that 'Furoxone' is a valuable drug for the treatment of gastro-enteritis and deserves further trial.

I wish to thank Smith Kline and French Laboratories Ltd. for a generous supply of 'Furoxone' and the record cards for the evaluation of results.

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ACROCEPHALOSYNDACTYLY OR APERT'S SYNDROME

REPORT OF A CASE

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Acrocephalosyndactyly (or Apert's syndrome) is a relatively rare condition. Among the 826 mentally retarded inmates at present at the Alexandra Institution, there is only one such case, the only one, as far as the writer is aware, since the Institution was opened in 1921 for the certifiable mentally retarded.

Recently Jones,[1] describing 2 cases, states that Sirkin in 1944 found only 5 cases in the American literature, but that since then several new cases have been reported. He also states that Weech described a case of a mother and her daughter who were afflicted with the same deformity and that Mohr recorded a family in which the father and 5 of his 9 children were affected.

Tredgold[2] and Hilliard and Kirman[3] in their respective excellent textbooks on mental deficiency (to which the interested reader is referred for more detailed information on this condition) in their descriptions of acrocephalosyndactyly mention one or several cases under their care.

This does not complete the list of known cases.

Owing to its rare occurrence and special interest one feels that the case of acrocephalosyndactyly at the Alexandra Institution warrants recording in a medical journal.

B. R., male European, born on 16 April 1951, was admitted to the Alexandra Institution as a certified mentally defective patient on 21 May 1951.

His parents are highly respectable, and physically and mentally very sound people. The father, a pensioner, is now 64, and the mother is 52 years old. They genuinely love their child and visit it frequently.

They gave the following history of B's case:

The mother was pregnant 3 times. The second pregnancy terminated in a miscarriage at 3 months. She attributes it to the strain produced by shifting heavy furniture about at the time. B is the youngest of the 2 living children. The other child, a boy of 11 years, was born by caesarean section because the mother's pelvis was contracted. He is perfectly normal in all respects, physically and mentally, is rather clever and always top of his class.

The parents are in no way related to each other. There is no history of any known mental abnormality in the father's or the mother's family. Both the parents always enjoyed excellent health, with the exception of the mother, who was not '100%' during her pregnancy with B. She was very depressed and irritable. During this pregnancy there was not even the slightest trace of any virus disease, e.g. German measles, etc. She had no accidents, no severe deprivations of any kind or any profound grief. She states that the child 'was apparently lying wrongly' and 'had to be turned by the doctor every month'.

B was also born by caesarean section. The operation took place 16 days before the expected date of birth. The mother was 44 and the father 56 years old when B was born. The father saw the baby immediately after birth, even before it had been washed, and already then the head had been 'horribly' deformed. 'I was terribly upset, I had never seen anything like it.' The doctor in attendance did not expect the child to live. It weighed 9 lb. at birth.

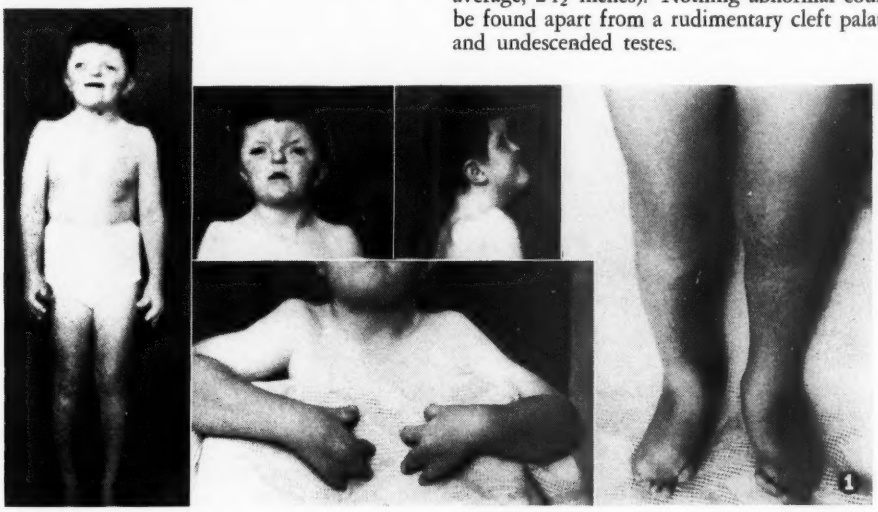
The baby was admitted to the Alexandra Institution when it was 35 days old. Its state of nourishment was described as fair, its weight was 8 lb. 8 oz., its height was 1 foot 8 inches and it was running a slight temperature (99.2° F.). It was found to have syndactyly of its hands and feet, also what was described as hydrocephalus. The anterior fontanelle was much enlarged. Physically nothing else was found wrong with the baby on admission. It was too young for an expression of an opinion about its mental condition.

A note in his case sheet dated May 1952, i.e. when he was a little more than one year old, reads as follows:

'He has grown much during the year and he weighs 23¾ lb. He is fed with a spoon now. He has one tooth, is a friendly baby and is able to recognize certain people in the ward. He can grasp things handed to him. He can sit up on his own if placed in a sitting position. His head gives the impression of having been squashed anteroposteriorly, the occiput being completely flat. The frontal protuberances bulge slightly, but the vertex is not pointed. He has a syndactyly of his hands and feet. His mental age appears to be that of a baby of 7 months.'

His general health was described as very good. Dr. Welsh, under whose care he then was, diagnosed his condition as acrocephaly with syndactyly, with questionable defective mental development.

During the following year there was still much evidence of delayed developmental data or milestones. He had not made the slightest attempt at walking, could only crawl and could not say any words. During his third year of life there was quite a lot of improvement in his condition. He could walk by himself in spite of the handicap of his syndactyly; he was able to say a few words; he was bright and most responsive to attention and much interested in his surroundings. He loved toys and played with them fairly intelligently. He had grown very big and fat.



After his condition had been discussed at a routine conference held by the medical staff of the Institution and its psychologist, the diagnosis was changed to hypertelorism. We know now that this diagnosis is wrong, and that there does not exist the slightest doubt that the original diagnosis of acrocephaly with syndactyly made by Dr. Welsh or acrocephalosyndactyly (Apert's syndrome) as it is generally known, is correct.

During the course of the following years there was a steady further improvement in the child's mental and general physical condition. He is now 8 years old and his present state is as follows:

His weight is 64 lb. 2 oz. (normal average, 54½ lb.), his height is 49 inches (normal average, 48 inches). His body is well covered and he enjoys very good general health.

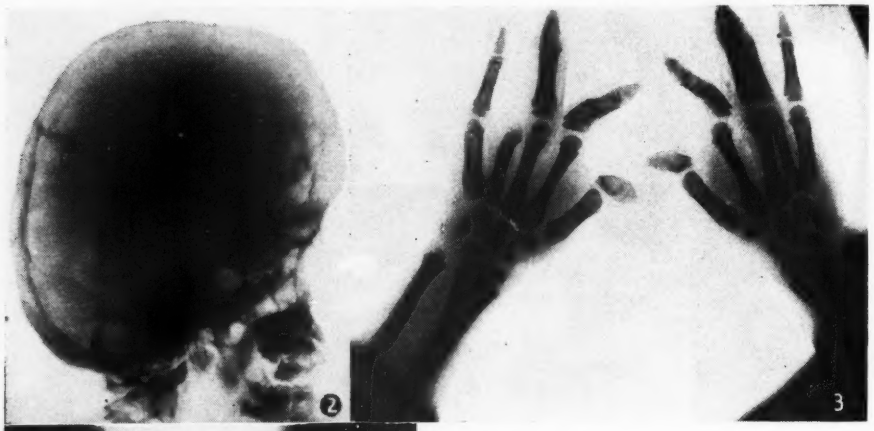
Of the usual childhood diseases, he has had only measles and in addition a few minor illnesses.

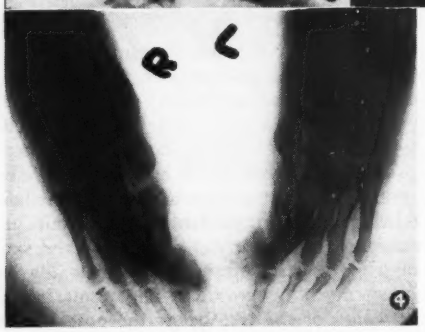
The very striking physical characteristics of his affliction are confined to his head, face, hands and feet (Fig. 1). The rest of his body is beautifully and proportionately formed, and actually is almost athletically developed with a chest circumference of 27 inches (normal average, 24½ inches). Nothing abnormal could be found apart from a rudimentary cleft palate and undescended testes.

His head and face are abnormally large for his body, but this deformity is quite distinctive from that of hydrocephalus. As so aptly expressed by Dr. Welsh, his head and face give the impression of having been taken anteroposteriorly between one's hands and forcibly squeezed together or squashed, so that the head and face are very much flattened out and broadened, the expansion of the face and skull being particularly upwards and bilaterally but not so much downwards. The result is that the region of the face below the nose is comparatively small. The frontal and occipital regions of the skull have much approached each other and tend to be parallel.

The occiput is virtually non-existent and feels almost as flat as a board. The top of the skull is not pointed, but rounded like a skullcap. The circumference of his head is 20¼ inches (normal average, 20¾ inches at 7 years), its antero-posterior diameter is 151 mm., bilateral diameter 142 mm., and its cephalic index, therefore, is 94 (hyperbrachycephalic).

His scalp is covered with thick coarse hair with one crown in front, another at the back of the scalp. The ears are or appear to be inserted low down on the sides of the face. His forehead bulges in the middle. The hair of his eye-brows is scanty. The eyes protrude very slightly and the intercuruncular distance is abnormally great, hyperteloric (45 mm., normally 30 mm. in a child of 9 years).[4] The palpebral fissures slope outwards and downwards (an 'anti-Mongolian' slant).[3] There is a slight squint; and occasional nystagmus when he looks up and sideways. His nose is small and beak-like; his mouth is small and usually gaping; his hard palate is narrow, high with a clearly visible rudimentary cleft palate. His teeth are good, but overlap each other in front; his chin is comparatively small. His hands and feet are badly deformed, fingers and toes being either fused or webbed to each other.





He can walk and run about as freely and well as any normal child in spite of the marked deformity of his feet. He feeds himself; he is clean and tidy in his person; he can undress himself and with his so badly deformed little hands, one is amazed to see how very skilfully he unbuttons his clothes without the slightest effort; he reveals the same dexterity with his hands with anything else he does. He requires some assistance when he dresses himself. He is (like most of the children here) very friendly, pleasant, polite, obedient, and loved by everyone in the Institution. He obeys simple commands promptly, converses readily and knows all the common objects about. He attends the very elementary school where he is considered one of the brighter pupils. He is very anxious to learn, can recite little poems, and can copy letters of the alphabet quite well. His I.Q. is about 50.

The X-ray films of his skull are very instructive and confirm much of what has already been said (Fig. 2), e.g. the elongated narrow skull with rounded, skull-cap top, the broadness of the facial part of the skull, the poor development of the air sinuses. The digital markings or copper-beaten appearance, so characteristic of acrocephalosyndactyly, are clearly seen, and, as Tredgold actually demonstrated at autopsy in such a case,[2] is due to a series of shallow depressions of the internal plate caused by the thinning of the skull. The thinness of the skull is well shown. The X-ray films of the hands (Fig. 3) and feet (Fig. 4) reveal the marked bony deformities. The hands were operated on with some success, although there still exists fusion and webbing between certain fingers.

His blood Wassermann reaction is negative.

Urinalysis, including a test with 5% ferric chloride solution (for the presence of phenyl-

pyruvic acid) is normal. The examination of the blood yielded:

Hb.: 65%;
Red Cell Count: 4.3 millions per c.mm.;
White Cell Count: 5,700 per c.mm.;
Differential leucocyte blood picture:
Basophils: 0% (0.5%).
Eosinophils: 1.7% (3%).
Juveniles: 0% (0%).
Stab-cells: 4.78% (4%).
Myelocytes: 0% (0%).
Segmented Cells: 37.32% (63%).
Lymphocytes: 53.42% (23%).
Monocytes: 3.08% (6%).

The normal average percentage is noted in brackets.

$$\text{Nuclear-Shift Index} = \frac{\text{Myelocytes + Juveniles + Stab-Cells}}{\text{Segmented Cells}} = \frac{0 + 0 + 4.78}{37.32}$$

= 0.12 (normally 0.06 in an adult living in a temperate climate as in Central Europe). (5)

Average Diameter of red cells = 7.4 microns.

DISCUSSION

Acrocephalosyndactyly is a rare affliction and, as far as the writer is aware, it has not yet been recorded in this country.

We know nothing about its cause. It is definitely a congenital condition. Some say that it is due to defective germ plasm; some instances indicate that heredity plays a part, but in other cases one cannot find the slightest clue with regard to its aetiology. Careful biochemical investigations may bring us nearer to a solution. It is also possible that exogenous factors during pregnancy play a part in its production.

In the case described here, the carefully taken history throws no light on the aetiology. The mother's age of 44, i.e. near the menopause, has scarcely any bearing on it. The mothers in Jones's 2 cases[1] were only 19 and 30 years old respectively. There is no reason that the 'wrong lie' the mother speaks about can be considered a causal factor.

Although the various developmental stages were much delayed during his first few years of life, since his third year he has been making striking progress in all respects and, in the opinion of our psychologist, has advanced intellectually far enough to be tried and given a chance at a not so elementary school outside the Institution. It is generally agreed that the mental defect in acrocephalosyndactyly is seldom gross, and that these patients usually respond well to training.[3]

SUMMARY

A case of acrocephalosyndactyly (Apert's syndrome) is described.

OPSOMMING

In die voorgaande artikel word 'n geval van akrokefalosindaktalia (Apert se sindroom) beskryf.

I must thank Dr. Pienaar, Commissioner for Mental Hygiene, and Dr. Cohen, Physician Superintendent of the Alexandra Institution, for permission to submit this article for publication.

I am deeply indebted to my colleagues Drs. Welsh and Terblanche, for their excellent notes on the patient's case sheet, and to Dr. Smith, psychologist, for valuable information.

I am very grateful to Mrs. Hueton, radiographer, Rondebosch and Mowbray Cottage Hospital, for the excellent X-ray films and to Mr. Swanepoel, Charge Nurse, for the photographs.

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RINGWORM (TINEA) INFECTIONS IN THE TRANSVAAL

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Ringworm varies a great deal from place to place, and even a few hundred miles away ringworm cases may have a different character. There is reason to suppose that this is also true in South Africa, though it is still regrettably a matter of hearsay. Moreover, the pattern may alter in the same place over a few years. For these reasons I am setting out here some clinical and mycological features of tinea infections seen consecutively in Pretoria over the period

1955–1958 inclusive. The record is admittedly imperfect, but it may serve for comparison with primarily clinical data from other areas.

The cases of tinea were distributed between tinea capitis (1.3%), tinea cruris (0.3%), tinea corporis (0.25%) and tinea pedis (0.75%), making 125 cases altogether, the percentage representing an approximate proportion of the total number of White skin patients seen in consultation by me over the same period. Fortunately, fungous infections in the Transvaal have never really been a serious problem, in the sense that the incidence was ever abnormally high, the disability severe, the site of infection awkward or species of fungus particularly tenacious. Tinea of the nails, e.g. was not seen during the period of study, and ringworm of the beard but once. *Trichophyton rubrum* nail infection and severe trichophytic granulomas of the beard have been observed here, but they are not endemic and were not seen in the period surveyed. With the discovery and recent marketing of griseofulvin, the burden of treatment promises to become much lighter, though, as always happens, other problems are thereby likely to be uncovered. Particularly, the eczematous and non-fungal character of many foot and groin eruptions is likely to become apparent, as well as possibly a sharper separation between saprophytic and pathogenic fungi, such as affect the nails for instance.

TINEA CAPITIS (63 CASES)

(*a*) *Proven and Presumed Cases of Microsporum canis Infection* (57 *Cases*). The sex incidence was about equal. By graphing the age incidence, some unexpected features became apparent (Fig.1). Firstly, the disease is not one of school-going age alone, but affects mainly the pre-school child with a maximum incidence at the age of 5; secondly, the insusceptibility of the adult to infection is represented by the end of the curve which starts declining after the age of 5 and approaches zero incidence during adolescence. It does not drop suddenly in adolescence, as has been supposed.

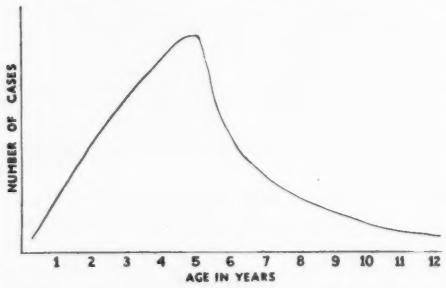

Fig. 1. Curve representing approximate frequency of *Microsporum canis* infection in 57 consecutive cases according to age.

In two thirds of the cases *M. canis* was isolated. In two thirds of the cases also there was an ostensible animal source of the infection equally divided between pet dogs and cats. When the source lay outside the child's home, the responsible animal was more commonly a cat. Judging from the histories, there were several cases of spread to other children in a household, away from the animal source, after the infection had been brought home by one child. School sources were implicated 3 times (once a Sunday school), but a proposed investigation of the schools excited little interest with some of the authorities. In all these instances of apparent child-to-child transmission in the home or school, *M. canis* was recovered.

In those cases presumed to be due to *M. canis* infection without proof by culture, the patients were classified here because of a fluorescent microsporon type of hair invasion, the history of an animal source and a clinical course like that in the proven cases. In some cultures where the fungus was isolated late in the disease, typical *M. canis* colonies and clinical findings otherwise closely comparable were seen, without macroconidia developing in the growth. Some strains then produced macroconidia on rice medium, but in others where this was not done, the balance of evidence seemed to favour the occurrence of a pleomorphic *M. canis* strain *in vivo* rather than the isolation of an identically pigmented *M. audouini*.

Cases where no animal or human source was known occasionally gave a history of local trauma. Buffeting the animals with the head served to combine the factors of contact and trauma, but ringworm was noted at the site of a fall on the scalp, after bruising the head on a bird cage, and from the scratch of a rake on the head. In one girl of $4\frac{1}{2}$, the ringworm was ascribed to taking a home perm.

Fluorescence under Wood's light was tested in all cases, and about a fifth of them showed none. Two causes for this were found: one was a type of case seen late in the disease with an alopecia areata-like picture and positive cultures; the other was due to suppurative change (kerion). Quenching of fluorescence with local applications was not a cause of absent fluorescence in the present series.

Most of the scalp ringworm infections were acquired in or around Pretoria, but a few cases seen from other parts of the Transvaal and the Orange Free State were identical. Most cases were seen within the first 3 months of the ailment and, in cases which did not develop suppuration, cure took 4–8 months altogether. Towards the end of the second month of the ringworm infection about a quarter of the cases developed suppurative changes varying from folliculitis and crusting to frank kerion with swollen regional glands. Cure was then evident within a few weeks. This delayed type of suppuration in *M. canis* infection contrasts with the primary kerion in *M. gypseum* cases.

Treatment. It seems that griseofulvin (0.5 to 1 g. daily by mouth for a few weeks) has almost overnight made scalp ringworm tractable, and X-ray epilation a thing of the past. In South Africa the use of X-ray epilation has often depended on the availability of a trouble-free radiotherapeutic service, though its advisability in a self-limiting condition was always debatable. In the past I have advised X-ray epilation only in those cases of non-suppurative *M. canis* infection who, under conservative treatment, showed a sudden starry fluorescence all over the scalp. The adequacy of this indication may even be questioned. If the ringworm is not suppurative, and whether griseofulvin is used or not, a cheap and simple measure is local epilation of the scalp with a commercial barium sulphide paste (e.g. Veet). It is easier to take off areas of scalp hair from a child in this way once a week than to try cutting or shaving. The paste is applied on and around the patch for about 5 minutes, and the infected hair, paste and all, is wiped off with gauze. When the area is clean a fungicidal paint (e.g. dilute iodine) can be applied. This routine should probably be advised in any case to limit the transmission of infection when griseofulvin is being given. Since the suppurative case does well in any event, local antiseptic treatment may be all that is necessary.

There has always been the possibility, with otherwise successful X-ray epilation in young children, of obscure damage to the skin and the brain. Electroencephalographic changes after epilation are now well attested, and recently I have treated a proven basal cell epithelioma in the hairy scalp of a lady who was successfully epilated in London at the age of 4 in 1910. This tumour was situated in the hair on the vertex in the midline, at the site of what may have been the centre of the field treated. It seemed to me that a coincidence was rather unlikely, since rodent ulcers are most unusual in this situation.

(*b*) *Trichophyton violaceum Infection* (4 *Cases*). Doubtfully fluorescing infection of the scalp due to *T. violaceum* was seen in 4 children, 2 of whom are alleged to have acquired it from a calf. In the other 2 the condition had been present for over a year, which distinguished it at once from the *M. canis* group. In some of the South African coastal towns it seems that *T. violaceum* infection is more prevalent, judging from verbal reports.

Epilation with X-ray was advised for cases in this group, but griseofulvin would be preferable today.

(*c*) *Microsporum gypseum Infection* (2 *Cases*). Two 4-year old children with immediately developing kerion caused by *M. gypseum* were seen. There was no fluorescence. These types of kerion, which occurred within 10 days of the onset, were obviously different from the delayed kerion of *M. canis* as described above.

(*d*) *Favus.* No White cases have been seen. At the Pretoria General Hospital one Coloured sufferer from favus was seen recently, a 14-year-old girl who had picked up the infection 3 years before in Port Nolloth. The picture was that of *witkop,* with a matted, beige-coloured, outer layer smelling of mice and which, on removal, revealed typical yellow-white scutula against the scalp underneath.

(*e*) *The Bantu. M. canis* scalp ringworm has been seen by us in the Bantu, but is less common than in the Whites. Bantu children are prone to an impetigo of the scalp which is often called ringworm in error, but its rapid spread with oozing and crusting, and no immediate hair loss (barring temporary or later cicatricial alopecia) help to differentiate it. Head lice do not seem to contribute to the start of impetigo, but the custom of shaving the scalp does.

TINEA BARBAE (1 CASE)

A kerionic tinea of the beard due to *Trichophyton mentagrophytes* was seen in a 36-year-old man who had been infected by a vervet monkey. This monkey successively infected 3 other families while it was passed on from one to the next like a counterfeit coin. In one of the children belonging to the 4th family, who was later seen at hospital by me, a confluent, scaling, erythrodermic tinea corporis had resulted. The child's mother felt too sorry to destroy the pet, and 'preferred to give it away to Hollanders'. We have heard nothing of it since.

TINEA CORPORIS (12 CASES)

Patients in this group were mostly children with dog or cat *M. canis* infection. The condition was transient, and was often present in the tinea capitis cases too, which are not counted here a second time. Sometimes a parent acquired a transient tinea corporis. The patches were often dry and pale, eczematized, or burnt by local applications. Punctate green fluorescence could often be detected in the lanugo hairs.

Generalized severe *T. mentagrophytes* infection was also brought to our notice a few years ago by Dr. R. Kooij in a patient seen by us in Pretoria with Cushing's disease. This case, like the similar one mentioned under tinea barbae above, was not included in the survey period but deserves mention here. Before Dr. Kooij suggested that fungi should be sought, I had diagnosed the condition wrongly as a case of Kyrle's disease. In the European and American cases of Cushing's disease with generalized fungous infection, *Trichophyton rubrum* has been more commonly isolated.

Three problematic adult cases of body ringworm were seen, all with strongly positive scrapings for fungi, in which the cultures gave some difficulty. One was a 47-year-old woman with a rapidly spreading, unilateral, submammary lesion like a tinea cruris. Another was a young man with an extensive plaque over one shoulder and the last had an 'eczematide migratrice' type of lesion on the shin. The last 2 roused suspicions of tuberculoid leprosy to the point even of having somewhat vacuolated histiocytes in the underlying granulomas at the edge of the lesion. They responded poorly to simple antifungal measures. The cultures in the first 2 cases gave no growth and in the last a possible pleomorphic *Trichophyton mentagrophytes* was recovered.

TINEA CRURIS (14 CASES)

In this group moniliasis and erythrasma are excluded.

Normally one sees rather few cases of tinea cruris in consultation, but it appears to be an exclusively postpubertal condition affecting particularly men in their early twenties. Evidence was gathered of spread in one household and in one boys' high school boarding house. In these instances the common laundering of clothes or the wearing of borrowed clothing (underpants, bathing trunks) were apparently responsible for the spread of infection. Many patients describe the chafing from rough, dirty or tight underpants, battledress, etc. as having precipitated the condition. Occasionally tinea corporis or pedis was seen in association.

In the first few weeks of an attack scrapings for fungus were positive, but after the second month, when healing, irritation, sepsis or eczematization had supervened, the results tended to be negative. All the cases showing no secondary dermatitis responded well to treatment, and in these a modified Castellani paint (virtually a phenol and resorcin formula from which the unaesthetic basic fuchsin dye had been left out) was frequently prescribed. In some patients, regardless of treatment a persistent tender redness or marked itching was seen to follow in the wake of the fungous infection, suggesting that an intertriginous seborrhoeic dermatitis had been provoked.

In most cases cultures were attempted but the slants were vexingly either sterile or contaminated by non-pathogens. In a case recently seen of tinea cruris in a woman (a rare occurrence), *Trichophyton mentagrophytes* was grown.

TINEA PEDIS (35 CASES)

The diagnosis of tinea pedis was based almost entirely on scrapings which were positive for fungus filaments (excluding mosaic fungus). A large number of cultures failed to grow, and the only successful ones yielded a typical or a pleomorphic *Trichophyton mentagrophytes*. Men comprised almost 90% of the cases, with a maximum age incidence in the 20–25 year period, the same as for tinea cruris. The condition was not seen before puberty, but the upper age limit extended up to the early 60s, due largely to persistent summer relapses over many years. This contrasts with tinea cruris, where relapses are far fewer, and my oldest male patient was 42.

Clinically the features of tinea pedis were not unusual, comprising small grouped blisters on the sole, toes and sides of the feet, often confluent, and associated with keratotic scaling, interdigital bursts and desquamation, often unilateral, and liable to sepsis, persistent tenderness and eczematous change. Subsequent ide eruptions on the fingers occurred 2–8 weeks after the onset of the foot trouble and were various in pattern—mild digital blistering, keratolysis exfoliativa, dysidrotic and bullous ides and centropalmar or thenarhypothenar palmar ides. An apparently primary pustulation was sometimes seen in the

foot lesions, particularly after the second month.

Injuries during river and sea bathing were sometimes blamed as precipitating causes of tinea pedis, as well as the more usual contact with shower-room floors, which seemed to be responsible in a boys' high school boarding house outbreak.

Treatment in the case uncomplicated by sepsis was carried out by removal of scale and blister roofs, either mechanically or by salicyclic acid, 10% in 70% alcohol, followed either by Castellani's paint or a paint with 1–3% chrysarobin and 10% liquor picis carbonis resembling the celebrated Arning's Tincture.

SUMMARY

One hundred and twenty-five consecutive cases of dermatophyte infection in White patients from the Transvaal are reported.

Features of the age and sex incidence, the commoner fungous pathogens, epidemiological, clinical and therapeutic findings are discussed.

OPSOMMING

Verslag word gedoen oor 125 agtereenvolgende gevalle van dematofiet-infeksie by blanke pasiënte in Transvaal.

Kenmerke van die ouderdoms en geslagsvoorkoms, die meer algemene swampatogene, en die epidemiologiese, kliniese en terapeutise bevindings word bespreek.

A CASE OF SUBACUTE PROGRESSIVE ENCEPHALITIS

WITH COMMENTS ON THE NATURE OF THE REPETITIVE COMPLEXES

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A case of subacute progressive encephalitis is described. As far as it is known, this is the first case of this condition to be reported from South Africa. It also seems appropriate to compare the typical complex potential that occurs in EEG records of such patients with similar potentials recorded during light sleep in normal individuals (the 'K' complex), with complexes sometimes accompanying the jerks of myoclonic epilepsy and with complexes recorded in the EEG of some patients with known organic damage to the midbrain.

CASE DESCRIPTION

Clinical History. The patient was a male child of 4 years admitted to the Transvaal Memorial Hospital for Children with a prior history of myoclonic jerking for the preceding 5 weeks. Myoclonus started suddenly and for the first 2 days the left side was especially affected, while the jerks occurred at intervals of about 10–15 seconds; later all 4 limbs, the neck and the back (but not the face, though there was occasional difficulty in chewing and swallowing) were affected whilst the jerks became more frequent, occurring about once every 5 seconds. At first speech was not involved, but for 2 weeks before admission the child had become progressively more silent so that he hardly spoke at all on admission. Likewise walking was possible at first, but at the time of admission the patient could neither walk nor sit up by himself. No oculogyric crises had been noted and there was no apparent depression of awareness. Myoclonus ceased during sleep but the child was tired from the persistent jerkings whilst awake.

The patient was admitted on 29 November 1954; on 4 December oculogyric crises were thought to be present and frequent petit mal-like lapses were noted, the clinical diagnosis at that time being paramyoclonus multiplex. By 22 January 1955 the pupils were dilated, equal and unresponsive to light; definite oculogyric crises were occurring; the face was mask-like; a coarse, slow (2–4 per second) tremor affected the wrists and was increased on movement; the arms and legs tended to assume the flexor attitude; deep reflexes were very brisk and equal on both sides, the abdominal and cremasteric reflexes were absent; tone was generally decreased in the legs, while the plantar reflex on each side was extensor. The child died on 20 February 1955.

A month before the onset of myoclonus, the child had been frightened by ants crawling over his legs and thereafter he had frequent tactile paraesthesiae, brushing imaginary insects off himself, especially at night. There seems little doubt that paraesthesiae marked the onset of subacute progressive encephalitis in this child.

The patient's birth history and subsequent development were entirely normal. Apart from measles and one convulsion in infancy there were no previous illnesses, certainly none that might be considered as precipitating subacute progressive encephalitis. There was no

history of a similar condition in the family of either parent.

The patient did not respond to any anticonvulsant, or to Largactil, or ACTH. Finally almost continuous sedation (and symptomatic treatment of its complications) was adopted.

Clinical Pathology. Specimens of cerebrospinal fluid and urine were repeatedly normal. The blood count likewise remained normal as did the blood proteins and inorganic ion constituents. Tests for liver function, of which 7 different methods were used, consistently showed liver damage even before continuous sedation was instituted. Coxsackie virus was not isolated from the cerebrospinal fluid while complement fixation tests on the blood for the viruses of herpes simplex, lymphocytic choriomeningitis, mumps, psittacosis, Rift valley fever, smallpox and vaccinia were all negative. The ESR was not raised.

Radiology. Skull X-ray films were entirely normal and plates of the wrists showed no decalcification.

Electroencephalography. Two records were taken during the first 3 weeks after admission. One was a waking record and the other was recorded while the child slept. Both records show the repetitive slow wave complexes (Fig. 1), but myoclonic jerks, coincident with the EEG complexes, occurred only when the patient was awake.

Each complex recorded in any one channel was generally similar to others occurring in that channel throughout the EEG. The waveforms and amplitudes were not so similar from channel to channel in the record. Each complex consisted of bilaterally synchronous and symmetrical single high voltage slow waves, or brief sequences of 2–3 of such waves, each wave having a period of between 0.3 and 0.6 second. The first slow wave of a sequence was usually of greater voltage than the others. The voltage of the complexes appeared to be greatest over the frontal and occipital regions, but this was probably an illusion created by using a common midline electrode over the nasion and one above the inion. The episodes did not block on eye opening. Complexes were repeated at intervals varying from 3 to 10 seconds though almost half the intervals were of about 5 seconds duration, 75% of the intervals falling between 5 and 7 seconds and over 90% between 4 and 8 seconds. No spikes or sharp components were seen.

The record between complexes was of relatively low voltage and generally somewhat featureless. Some remnants of alpha rhythm were seen in the waking record, but there was more 5–7 c.p.s. theta rhythm, interspersed with many irregular potentials, distributed in the central and postcentral regions with an occasional encroachment over the frontal cortex. The theta rhythm blocked poorly on eye opening. The relative proportion of theta rhythm and of irregular low voltage slow activity was distinctly in excess of that expected at the age of $4\frac{1}{2}$ years with signs of an alpha rhythm present.

In the sleeping record a moderate amount of low voltage 18–20 c.p.s. barbiturate fast rhythm was seen postcentrally, but its incidence was significantly less over the left parietal and temporal cortices compared with the homologous areas on the right. (In the waking record theta activity was somewhat more abundant over the left postcentral regions). Later in the sleeping record, 9–10 c.p.s. frontal sleep spindles occurred symmetrically.

Thus the record between complexes was not grossly abnormal though there was an indication of patchy cortical and subcortical damage, more especially in the postcentral regions of the left hemisphere.

On the basis of the foregoing findings, the conclusion to one of the EEG reports read as follows:

'The EEG is virtually diagnostic of subacute encephalitis (as described by Drs. Hill and Cobb from the National Hospital, London). A better descriptive term might be subacute encephalopathy'.

Pathology. Pathological details were kindly supplied by Dr. Neville Proctor.

'At the post-mortem there was nothing of note in the general examination except a quite well marked hypostatic congestion of the lungs. On opening the skull and dura the brain was abnormal in consistency. It was yellow, rubbery and some areas were firmer than others. I took out a piece for virus studies which has come back negative. I also took a piece for section. The spinal cord appeared normal'.

Later Dr. Proctor reported that the histological appearance was that described by Greenfield in subacute progressive encephalitis and added that:

'In the cases Greenfield described there were many very diffuse lesions involving cortex, midbrain, basal ganglia, spinal cord, etc.'.

DISCUSSION

The feature of the EEG in this condition that is emphasized here is the individual complex, repeated with an unusually long-term periodicity.

While the EEG record is probably diagnostic, as Hill and Cobb[2] believe, it would seem that diagnostic specificity is not conferred by the wave form of the individual complexes

but rather by the relative regularity with which they recur, at intervals that are prolonged for EEG events, as well as by the arrhythmic and featureless nature of the record between complexes. It is contended that the range of wave form of the complexes is indistinguishable from that of 'K' complexes occurring especially in response to auditory stimuli during light sleep, and also from the random cerebral potentials often recorded from patients suffering from midbrain damage (usually post-traumatic in the broad sense) from other causes, who display degrees of the 'midbrain state' described by Cairns.[1] In records from some patients afflicted with photically induced myoclonic jerks, similar complex wave forms are related to some or all of the jerks; these wave forms are not merely movement artefacts.

It is all but certain that the complex potentials described in the latter conditions reflect liminal and subliminal changes in the membrane potential of a very large number of cortical neurones. It is only slightly less likely that the changes in the cortical neurones are initiated by impulses originating in subcortical regions. It seems probable that, for each of the complexes enumerated in the previous paragraph, the originating mechanism lies within the midbrain. It may be supposed, as a corollary, that during the phase of subacute progressive encephalitis in which the EEG contains a repetitive series of more or less similar wave forms the midbrain is fairly extensively, if not entirely, involved in the disease process.

The evidence for the mesencephalic origin of the various complexes that is derived from records of patients with severe midbrain damage is the most direct, though it is not conclusive. In the case of 'K' complexes it seems significant that the latency between stimulus and the appearance of the complex on the EEG is prolonged (usually several seconds) and is of the same order as the time interval between repetitive complexes in subacute progressive encephalitis. The latency of the 'K' complex argues for an indirect and subcortical pathway for the relay of neuronal activity to the cortex after an auditory stimulus occurring during light sleep. On neuroanatomical grounds the midbrain reticular formation is the most likely site for the greater part of the indirect pathway postulated. Similarly it is reasonable to conjecture that 'K-like' complexes occurring with photically evoked myoclonus result from stimulation of the midbrain tectum and reticular formation via the optic tract. Indeed, in very light sleep, 'K' complexes are at times coincident with a type of myoclonic jerk, while similar jerks sometimes occur in patients afflicted with severe and at least partially irritating midbrain damage from various causes. Finally, the clinical presentation of patients, when awake, in all but the terminal phases of subacute progressive encephalitis might be described as 'status myoclonus,' provided the latter term is not regarded as a nosological entity or related to any form of epilepsy of cortical origin.

The complexes of subacute progressive encephalitis, 'K' complexes and the complexes associated with severe midbrain damage are

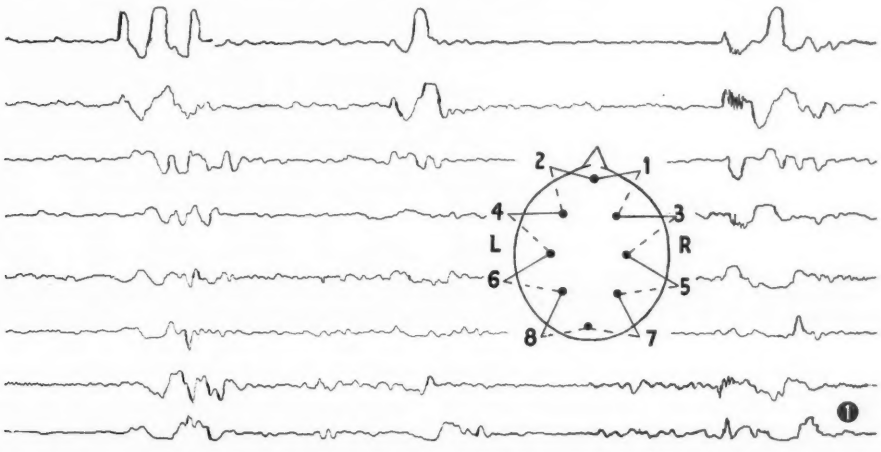

Fig. 1. Extract of the EEG of a case of subacute progressive encephalitis taken while the patient was awake. The first and third complexes have some accompanying movement artefact since each complex was associated with a myoclonic jerk affecting the axial musculature especially.

not associated with myoclonic jerks if the patient is asleep, but they may be coincident with jerks if the patient is 'drowsy' or if he is awake. Thus the depth of sleep influences the coincidence of EEG complex and myoclonic jerk whether the person is diseased or merely near the borderland between sleep and wakeful awareness. As far as is known, none of the 3 types of complex is influenced by anticonvulsant medication. It would seem that the pathway from the midbrain to the cortex is not impeded by sleep or drugs, but that the path between the cortex and the lower motor neurone (or perhaps the path between the midbrain and the lower motor neurone) is blocked during all but the lightest degrees of sleep, whether sleep is natural or induced by hypnotics.

SUMMARY

1. A case of subacute progressive encephalitis occurring in a South African European child of 4 years of age is described.

2. Tactile paraesthesiae preceded the myoclonic phase of the illness by about one month.

3. All attempts to isolate a virus proved negative.

4. The EEG is considered to be diagnostic in most phases of this illness on the grounds of the relatively regular repetition of complex, high voltage, slow wave potentials rather than on the nature of the slow wave potentials *per se*.

5. The complexes recorded in cases of subacute progressive encephalitis are compared with 'K' complexes, with similar potentials often recorded in the EEG of patients suffering from organic midbrain damage and with potentials sometimes associated with photically evoked myoclonic jerks.

OPSOMMING

1. 'n Geval van subakute progressiewe harsingontsteking by 'n blanke, 4-jarige Suid-Afrikaanse kind word beskryf.

2. Die miokloniese fase van die siekte is omtrent 'n maand tevore deur taktiele parestese voorafgegaan.

3. Alle pogings om die virus te isoleer, was negatief.

4. Die EEG word as diagnosties beskou in die meeste fases van hierdie siekte op grond van die betreklik reëlmatige herhaling van komplekse, hoogspannings-, trae-golf-potensiale, liewer as op grond van die aard van die trae-golf-potensiale *per se*.

5. Die komplekse, aangeteken in gevalle van subakute progressiewe harsingontsteking, word vergelyk met 'K'-komplekse, met dergelike potensiale wat dikwels aangetref word in die EEG van pasiënte lydende aan organiese middelbreinbeskadiging, en met die potensiale wat soms geassosieer is met miokloniese rukkings wat foties teweeggebring word.

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1. Cairns, H. (1952): Brain, **75**, 109.
2. Hill, D. and Cobb, W.A. (1950): Brain, **73**, 392.

PREPARATIONS AND APPLIANCES

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Published fortnightly by the Proprietors Juta and Co. Ltd., 43 Pritchard Street, Johannesburg, and printed in the Union of South Africa by Cape Times Limited, Parow, C.P.